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### Functional role for the UDP-glucuronosyltransferases (UGTs) in melanoma drug resistance

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The UGT family of enzymes catalyzes the glucuronidation and clearance of several anti-cancer agents. UGTs are expressed primarily in the liver, but are also expressed in several extra-hepatic tissues including prostate, breast, colon, lung, brain, kidney, bladder and ovary. However, there have been no reports of UGTs in melanocytes or melanoma. Our objective was to ascertain the role of UGTs in melanocytes and melanoma. We screened several primary melanocyte cultures as well as several melanoma cell lines for UGT expression by RT-PCR. TaqMan Real time PCR assays were used to determine UGT expression in melanoma cells before and after drug treatment. MTT assays were employed to determine IC50 values and UGT-Glo assay was used to measure UGT activity. Three UGT family members, UGT2B7, UGT2B10 and UGT2B15, were found to be expressed in melanocytes. Interestingly, of all the melanoma cell lines screened only WM115, a primary melanoma, had UGT expression. Again, only UGT2B7, UGT2B10 and UGT2B15 were detected. UGT expression was not detected in another primary melanoma cell line, WM3211, or in any metastatic melanoma cell line assayed indicating that loss of UGT expression occurs during melanoma progression. Treatment of melanoma cells lacking UGT expression (WM3211, SKmel28 and A375) with an anti-cancer agent (temozolomide, adriamycin, or epirubicin) induced expression of UGT2B7, UGT2B10 and UGT2B15 in these cells. Furthermore, UGT activity assays show increased glucuronidation in melanoma cells following treatment with an anti-cancer agent. Finally, knockdown of UGT2B7 in WM115 cells sensitized these cells to epirubicin and adriamycin treatment, but not temozolomide treatment. UGTs are expressed in melanocytes and their expression can be induced in melanoma cells. Since the UGTs are Phase II drug metabolism enzymes, we hypothesize that the upregulation of the UGTs in melanoma cells in response to anti-cancer agents is a potential mechanism for the well documented drug resistance observed in melanoma. Our observed results that knockdown of UGT2B7 sensitizes melanoma to epirubicin and adriamycin, but not temozolomide treatment supports our hypothesis since both epirubicin and adriamycin are substrates for UGT2B7 while temozolomide is not. We conclude that future anti-cancer drug strategies for melanoma will have to account for tumor cell mediated glucuronidation.